Please replace the paragraph beginning at page 4, line 30, with the following amended paragraph.

First three immunomodulating properties of type I IFNs (inhibition of lymphocyte proliferation after stimulation with lectins or allogenic cells, prolongation of skin grafts, and inhibition of delayed type of hypersensitivity) are useful for amplification of immunosuppressants' (cyclosporins, FK506 and rapamycin) activity. But other immunomodulating properties of type I IFNs (differentiation towards a Th1 type of immune response; stimulation *in vivo* of long-lived antigen-specific memory $CD8^+$ cell cytotoxicity; inhibition of suppressor T cells; enhancement of NK cell cytotoxicity; enhancement of MHC class I antigens expression) can induce an opposite effect. Indeed, it was observed that a monoclonal antibody directed against the extracellular domain of the human (h) IFN-α receptor, which inhibits both the binding and biological activity of all the type I IFNs tested, exerted a dose-dependent inhibition of the mixed lymphocyte reaction and induced permanent survival of skin allografts in MHC-divergent Cynomologus monkeys treated with a subeffective dose of cyclosporin A (Tovey, M.G. et al, 1996, J. Leukocyte Biol. 59, pp. 512-517).

Please replace the paragraph beginning at page 5, line 13, with the following amended paragraph.

C3

In the present invention we suprisingly observed that the physiological effects of immunosuppressants (cyclosporins, FK506 and rapamycin) can be dramatically increased by the simultaneous administration of any one of the immunosuppressants and the peptide corresponding to the high-affinity binding/anti-lymphoproliferative site of IFN α or the recombinant protein having the amino acid sequence corresponding to the said site. Peptides are specially favourable additives since they do not cause harmful symptoms and the acitivity quenching due to the generation of antibodies against larger polypeptides such as natural interferons.

Please replace the paragraph beginning at page 5, line 22, with the following amended paragraph.

C4

Long time ago there was discovered the primary structure homology of hIFNsα/β and thymus hormone - thymosin α_1 ($Tm\alpha_1$) (Zav'yalov V. and Denesyuk A., 1984, Doklady Akademii Nauk SSSR 275, pp. 242-246). Comparison of the primary structures of proTMα and hIFNsα/β reveals a homology of the prohormone with the IFNs' sites making up the C-terminal helices D and E, however, the highest homology is observed for the C-terminal part of helix D and the N-

terminal part of loop DE (Zav'yalov V. et al., 1989, Immun. Lett. 22, pp. 173-182; Zav'yalov V. et al., 1990, Biochim. Biophys. Acta 1041, pp.178-185). One of the synthesized peptides (α-peptoferon) overlapping the $TM\alpha_1$-like sequence of hIFN-α2, effectively competed with hIFN-α2, $TM\alpha_1$, proTMα for common receptors on mouse thymocytes (i.e. the K_i of recombinant (r)hIFN-α2 binding by α-peptoferon is equal to about 10^{-12} M) (Zav'yalov V. et al., 1991, FEBS Lett. 278, pp. 187-189; Zav'yalov V. et al., 1995, Molec. Immun. 32, pp. 425-431). Recently the first example of successful grafting of hIFN-α2's $TM\alpha_1$-like site to the design *de novo* protein albeferon was described (Dolgikh D. et al., 1996, Protein Engin. 9, pp. 195-201). The IFN-α2 fragment corresponded to the $TM\alpha_1$-like sequence 130-137 was inserted into the N-termini of an albebetin molecule just after the initiatory Met residue. The chimeric protein (albeferon) was expressed in a wheat germ cell-free translation system and tested for its compactness and stability. It has been shown that albeferon is practically as compact as natural proteins of corresponding molecular weight and possesses high stability toward the urea-induced unfolding. To testify the affinity of albeferon to murine thymocyte receptor, the protein inhibitory effect on the binding of radiolabeled [^{125}I] α-peptoferon to the receptors has been studied.

The albeferon competitive inhibition coefficient (IC_{50}) and the calculated inhibition constant (K_i) are very close to that of rhIFN-α2. It was demonstrated that cell surface binding characteristics correlate with consensus type I IFN enhanced anti-lymphoproliferative activity on the human periferal polymorphonuclear cells (Klein S. et al., 1996, J. Interferon and Cytokine Res. 16, pp. 1-6; Dhib-Jalbut S. et al., 1996, J. Interferon and Cytokine Res. 16, pp. 195-200).

Please replace the paragraph beginning at page 6, line 18, with the following amended paragraph.

The present invention includes the compositions for efficient amplification of immunosuppressive activity of cyclosporins, FK506 or rapamycin by peptides corresponding to the high-affinity binding/anti-lymphoproliferative site of IFNs-α, β, ω, τ or recombinant proteins having the amino acid sequences corresponding to the said site to decrease therapeutic dose of the both groups of compounds, and as the consequence to avoid their undesirable side effects during organ and tissue transplantation, and treatment of different diseases.

C5

Please replace the paragraph beginning at page 7, line 4, with the following amended paragraph.

C6 These compositions include cyclosporins, FK506 or rapamycin and biologically active peptides corresponding to the high-affinity binding/anti-lymphoproliferative site of IFNs-α, β, ω, τ, or recombinant proteins having the amino acid sequences corresponding to the said site.

Please replace the paragraph beginning at page 7, line 11, with the following amended paragraph.

C7 FIG. 1 Effect of rhIFN-α2 and of the peptide corresponding to the high-affinity binding/anti-lymphoproliferative site of hIFN-α2 (α-peptoferon) on mitogen (PHA)-driven proliferation of human peripheral polymorphonuclear cells.

Please replace the paragraph beginning at page 7, line 15, with the following amended paragraph.

C8 FIG. 2 Effect of rhIFN-α2 and of the peptide corresponding to the high-affinity binding/anti-lymphoproliferative site of hIFN-α2 (α-peptoferon) on the proliferation of an IFN-sensitive human T-lymphoblastoid cell line MT-4.

Please replace the paragraph beginning at page 7, line 19, with the following amended paragraph.

C9

FIG. 3 Effect of rhIFN-α2, albeferon and albebetin on mitogen (PHA)-driven proliferation of human peripheral polymorphonuclear cells.

Please replace the paragraph beginning at page 7, line 22, with the following amended paragraph.

C10

FIG. 4 Effect of rhIFN-α2, albeferon and albebetin on the proliferation of an IFN-sensitive human T-lymphoblastoid cell line MT-4.

Please replace the paragraph beginning at page 7, line 25, with the following amended paragraph.

C11

FIG. 5 Effect of rhIFN-α2 and of the peptide corresponding to the high-affinity binding/anti-lymphoproliferative site of hIFN-α2 (α-peptoferon) on mitogen (PHA)-driven proliferation of human peripheral polymorphonuclear cells in the presence of 20 mM cyclosporin A in cultural medium.

Please replace the paragraph beginning at page 8, line 11, with the following amended paragraph.

In this invention, there was surprisingly observed that certain favourable physiological effects of cyclosporins, FK506 and rapamycin on human cells can be amplified by biologically active peptides corresponding to the high-affinity binding/anti-lymphoproliferative site of IFNs-α, β, ω, τ or recombinant proteins having the amino acid sequences corresponding to the said site. The peptides and recombinant proteins mentioned above can be readily produced by widely available synthetic or recombinant techniques. The present invention provides definite improvement of compositions for drugs based on cyclosporins, FK506 or rapamycin aimed for human and higher animals. These compositions include the immunomodulators and biologically active peptides corresponding to the high-affinity binding/anti-proliferative site of IFNs-α, β, ω, τ, or recombinant proteins having the amino acid sequences corresponding to the said site. Although all the potentially bioactive peptides or the recombinant proteins containing the amino acid sequences of the peptides were not possible to test experimentally here with the immunomodulator drugs (cyclosporins, FK506 and rapamycin) such structures were revealed by extensive comparisons of available amino acid sequences of interferons from different species by computer and molecular modelling techniques taking into account the experimental data on the localisation of the high-affinity binding/anti-

lymphoproliferative site of IFNs-α, β, ω, τ and the experimental data on the competition of type I IFNs for the common receptors. The peptides according to this invention have the advantage of not give rise to antibodies like large polypeptides and natural interferons and thus pepetides as such or bound to carrier molecules can be used for long periods.

Please replace the paragraph beginning at page 9, line 1, with the following amended paragraph.

In the previous studies (Zav'yalov V. et al., 1991, FEBS Lett. 278, pp. 187-189; Zav'yalov V. et al., 1995, Molec. Immun. 32, pp. 425-431) it was demonstrated that only octapeptide corresponding to the 130-137 amino acid residues of hIFN-α2 had the same or higher affinity to the specific receptors in comparison with recombinant hIFN-α2. It is well-known that all type I IFNs compete for the common receptors and can induce the common type I IFN activities. Therefore, it is reasonable to assume that in the process of natural selection the changes in the amino acid sequence of the high-affinity binding/anti-lymphoproliferative site of IFNs-α, β, ω, τ were selected not to abolish the biological activities of the site. Consequently, all type I natural and recombinant IFNs as well as peptides corresponding to their high-affinity binding/anti-

lymphoproliferative site, and recombinant proteins having the amino acid sequences corresponding to the said site might reproduce the anti-proliferative activity and amplify immunosuppressive activity of cyclosporins.

Please replace the paragraph beginning at page 9, line 14, with the following amended paragraph.

C 14

For the testing of synergism of cyclosporin, FK506 or rapamycin and peptides corresponding to the high-affinity binding/anti-lymphoproliferative site of IFNs-α, β, ω, τ or recombinant proteins having the amino acid sequences corresponding to the said site we employed the classic anti-lymphoproliferative test system with human peripheral polymorphonuclear cells and human T-lymphoblastoid cell line MT-4. The cell culture conditions and the conditions of the humoral cells in blood circulation are closely related. In fact, in cell cultures, which are commonly used for testing of potential drugs, the conditions are strictly maintained similar to the blood circulation as to the temperature, pH, buffer, minerals, CO_2 and O_2 partial pressures and so on. On the other hand, in this special case the target cells of cyclosporins or the other immunosuppressants and the peptides corresponding to the high-affinity binding/anti-lymphoproliferative site of IFNs-α, β, ω, τ or recombinant proteins

having the amino acid sequences corresponding to the said site being used as the drugs exist specifically in the blood circulation in very equal conditions to the cell cultures. Thus, it is highly predictable that the drug compositions of the present invention can be used as medical drugs for purposes previously used for immunosuppressants alone as the active ingredient in the drug formulations.

Please replace the paragraph beginning at page 9, line 31, with the following amended paragraph.

C15

While the main experimental proof of the present invention lies on the use of peptides corresponding to the high-affinity binding/anti-lymphoproliferative site of IFNs-α, β, ω, τ or recombinant proteins having the amino acid sequences corresponding to the said site with cyclosporins, also FK506 and rapamycin can be applied with related amplification effect as with cyclosporins. Although the present invention describes effects of peptides corresponding to the high-affinity binding/anti-lymphoproliferative site of IFNs-α, β, ω, τ or recombinant proteins having the amino acid sequences corresponding to the said site on immunosuppressants such as cyclosporins, FK506 and rapamycin, it is evident that the peptides corresponding to the high-affinity binding/anti-

lymphoproliferative site of IFNs-α, β, ω, τ or recombinant proteins having the amino acid sequences corresponding to the said site will increase equally well the activities of any other immunosuppressant.

Please replace the paragraph beginning at page 11, line 10, with the following amended paragraph.

C16

Fig. 1 displays, respectively, the effect of rhIFN-α2 and of the peptide corresponding to the high-affinity binding/anti-lymphoproliferative site of hIFN-α2 (α-peptoferon) on mitogen (PHA)-driven proliferation of human peripheral polymorphonuclear cells. PHA induced strong lymphoproliferative response that was inhibited by rhIFN-α2 and α-peptoferon in a dose-dependent fashion. rhIFN-α2 and α-peptoferon demonstrated comparable effects. RhIFN-γ had either no effect or a minimal enhancing effect on the lymphoproliferative response. (1) rhIFN-α2; (2) α-peptoferon; (3) control: PHA; (4) control: cultural medium.

Please replace the paragraph beginning at page 11, line 20, with the following amended paragraph.

C17

Fig. 2 shows the effect of rhIFN-α2 and of the peptide corresponding to the high-affinity binding/anti-lymphoproliferative

site of hIFN-α2 (α-peptoferon) on the proliferation of an IFN-sensitive human T-lymphoblastoid cell line MT-4. The proliferation of human T-lymphoblastoid cell line MT-4 was inhibited by rhIFN-α2 and α-peptoferon in a dose-dependent fashion. rhIFN-α2 and α-peptoferon demonstrated comparable effects. Similar methods as in Example 1 were employed. (1) rhIFN-α2; (2) α- peptaferon.

Please replace the paragraph beginning at page 11, line 28, with the following amended paragraph.

Fig. 3 displays the effect of rhIFN-α2 and the designed *de novo* chimeric protein albeferon containing the TMα$_1$-like sequence 130-137 of the hIFN-α2 inserted into the N-termini of the protein just after the initiatory Met residue (2), and the designed *de novo* protein albebetin without the hIFN-α2 fragment (3) on PHA-driven proliferation of human peripheral polymorphonuclear cells. PHA induced strong lymphoproliferative response that was inhibited by rhIFN-α2 and albeferon in a dose-dependent fashion. rhIFN-α2 and albeferon demonstrated comparable effects. Albebetin had no effect on the lymphoproliferative response. The results show that the hIFN-α2 fragment corresponded to the TMα$_1$-like sequence 130-137 is responsible for the anti-lymphoproliferative effect of rhIFN-α2.

C 18

Similar methods as in Example 1 were employed. (1) rhIFN-α2 (2) albeferon; (3) albebetin; (4) control: cultural medium; (5) control: PHA.

Please replace the paragraph beginning at page 12, line 9, with the following amended paragraph.

Fig. 4 demonstrates the effect of rhIFN-α2, albeferon and albebetin on the proliferation of an IFN-sensitive human T-lymphoblastoid cell line MT-4. The proliferation of human T-lymphoblastoid cell line MT-4 was inhibited by rhIFN-α2 and albeferon in a dose-dependent fashion. In this experiment albeferon had higher activity than the sample of rhIFN-α2 used but comparable with other data on rhIFN-α2 (see Figs. 1-2 and the data described in: Dhib-Jalbut S. et al., 1996, J. Interferon and Cytokine Res. 16, pp. 195-200). Albebetin had no effect on the lymphoproliferative response. The results show that the hIFN-α2 fragment corresponded to the TMα_1-like sequence 130-137 is responsible for the anti-lymphoproliferative effect of rhIFN-α2. (1) rhIFN-α2; (2) albeferon; (3) albebetin.

Please replace the paragraph beginning at page 12, line 20, with the following amended paragraph.

Fig. 5 displays the effect of rhIFN-α2 on PHA-driven proliferation of human peripheral polymorphonuclear cells in the presence of 20 mM cyclosporin A (CsA) in cultural medium. PHA induced strong lymphoproliferative response. The selected concentration of CsA had enhancing effect on the lymphoproliferative response. The administration of extremely low amount of rhIFN-α2 (10^{-16} M) totally abolished lymphoproliferative response induced by PHA. The comparable effect on mitogen-driven proliferation of peripheral blood human T-lymphocytes in the presence of 20 mM CsA in cultural medium was observed for the octapeptide corresponding to the high-affinity binding/anti-lymphoproliferative site of hIFN-α2 (α-peptoferon). The results demonstrate strong synergism of anti-lymphoproliferative action of CsA and rhIFN-α2 or the peptide corresponding to the high-affinity binding/anti-lymphoproliferative site of hIFN-α2 (α-peptoferon). Related results were obtained with 1-50 mM concentration of FK506 or rapamycin instead of cyclosporin A. Similar methods as in Example 1 were employed. (1) rhIFN-α2 and 20 mM CsA; (2) α-peptoferon and 20 mM CsA; (3) control: cultural medium; (4) control: 20 mM CsA; (5) control: PHA; (6) control: 20 mM CsA and PHA.

Please replace the paragraph beginning at page 13, line 5, with the following amended paragraph.

Fig. 6 displays the effect of albeferon on PHA-driven proliferation of human peripheral polymorphonuclear cells in the presence of 10 mM cyclosporin A (CsA) in cultural medium. PHA induced strong lymphoproliferative response. The selected concentration of CsA had enhancing effect on the lymphoproliferative response. The administration of extremely low amount of albeferon (10^{-12} M) totally abolished lymphoproliferative response induced by PHA. Related results were obtained with 1-50 mM concentration of FK506 or rapamycin instead of cyclosporin A. Fig. 6 also shows that the octapeptide corresponding to the high-affinity binding/anti-lymphoproliferative site of hIFN-α2 (α-peptoferon) which was genetically immobilized on the macromolecular carrier (i.e. on the *de novo* protein albebetin) is biologically active. Similar methods as in Example 1 were employed. (1) albeferon; (2) albeferon and 10 mM CsA; (3) control: cultural medium; (4) control: PHA; (5) control: PHA and 10 mM CsA.

Please replace the Sequence Listing filed May 25, 2001 with the Substitute Sequence Listing enclosed herewith.